3-Methylamino-1-(2-thienyl)-1-propanone, its preparation and use

Description

3-Methylamino-1-(2-thienyl)-1-propanone, its preparation and use

The present invention relates to the preparation and use of 3-methylamino-1-(2-thienyl)-1-propanone.

The amino alcohol 1 (Fig. 1) [(1S)-3-methylamino-1-(2-thienyl)propan-1-ol] is a sought-after intermediate in the preparation of a pharmaceutical ((+)-(S)-N-methyl-3-(1-naphthyloxy)-3-(2-thienyl)propylamine oxalate – trade name Duloxetine®). The method which has been used thus far for preparing this intermediate is elaborate and requires expensive and labile reagents. Furthermore, a technically elaborate chromatography is required for preparing a pure compound. See, for example, EP 273658 A1; Liu et.al., Chirality 2000, 12 (1), 26-29; Wheeler et.al, J. Labelled Comp. Radiopharm. 1995, 36(3), 213-23; US 5362886, EP 457559, Deeter et al , Tet. Lett. 1990, 31(49), 7101-4; EP 0650965; L.A. Sorbera, R.M. Castaner, J. Castaner, Drugs of the Future 2000, 25(9): 907-916.

The object therefore was to make available simpler and more economical processes for preparing Duloxetine®.

The present invention describes novel and economical processes for obtaining the isomerically pure compound 1. As an intermediate which they share in common, the processes according to the invention use the novel ketone 5 (Fig. 1) [3-methylamino-1-(2-thienyl)-1-propanone], from which the amino alcohol 1 can be obtained by means of enantioselective reduction. The subsequent reaction of the aminoalcohol 1 to give Duloxetine® is well known to the skilled person and can be carried out in analogy with the process described in EP 0457559 A2 (reaction with 1-fluoronaphthalene).

The invention relates to 3-methylamino-1-(2-thienyl)-1-propanone (Fig. 1, compound 5) and its acid addition salts. The acid addition salts of compound 5 are products of the reaction of compound 5 with inorganic or organic acids. Acids which are particularly

suitable for this purpose are hydrochloric acid, sulfuric acid, phosphoric acid, oxalic acid, fumaric acid, maleic acid and acetic acid.

The starting compound for preparing the ketone 5 or the amino alcohol 1 can be thiophene or 2-acetylthiophene. Fig. 1 depicts three routes for preparing the ketone 5 (routes 1 to 3), which routes are described below:

Route 1

Compound 4 is obtained by way of a classical Mannich reaction starting with acetylthiophene, formaldehyde and dimethylamine (EP 0457559 A2 Example 1). The monomethylamino ketone 5 is obtained by means of a retromichael/Michael reaction, by reacting 4 with an excess of methylamine.

Route 2

Compound 6 is obtained by means of a classical Mannich reaction starting with acetylthiophene, formaldehyde and methylamine (Blicke; Burckhalter; JACSAT; J. Amer. Chem. Soc.; 64; 1942; 451, 453). The monomethylamino ketone 5 is obtained by means of a retromichael/Michael reaction, by reacting 6 with an excess of methylamine.

Route 3

The compound 7 is obtained by means of a classical Friedel-crafts acylation of thiophene 8 with 3-chloropropionyl chloride (described in El-Khagawa, Ahmed M.; El-Zohry, Maher F.; Ismail, Mohamed T.; PREEDF; Phosphorus Sulfur; EN; 33; 1987; 25-32). The monomethylamino ketone 5 is obtained by reaction with methylamine.

The invention also relates to the use of 3-methylamino-1-(2-thienyl)-1-propanone or its acid addition salts for preparing N-methyl-3-(1-naphthyloxy)-3-(2-thienyl)propylamine, or its acid addition salts, in racemic or enantiomerically pure form. Particular preference is given to the use for preparing (+)-(S)-N-methyl-3-(1-naphthyloxy)-3-(2-thienyl)propylamine oxalate (Duloxetin®).

The invention also relates to a process for preparing N-methyl-3-(1-naphthyloxy)-3-(2-thienyl)propylamine, or its acid addition salts, in racemic form or, preferably, in enantiomerically pure form, with 3-methylamino-1-(2-thienyl)-1-propanone or its acid addition salts being prepared as intermediate in a first step with this intermediate then being reduced to the corresponding alcohol.

The reduction can be carried out either under racemizing conditions or enantioselectively. Preference is given to an enantioselective reduction, in particular to such a reduction which yields the (S)-enantiomer 1 as the product.

This can be carried out either chemically, using classical enantioselective hydrogenation methods, such as using $NaBH_4$ or $LiAlH_4$, which are provided with chiral ligands for the purpose of achieving enantioselectivity, or using transition metal-containing hydrogenation catalysts or using enzymic reductions, for example using microbial, in particular bacterial or fungal, dehydrogenases.

Experimental:

Route 1:

5 g of dimethylamino ketone 4 are initially introduced as the hydrochloride in 25 ml of ethanol after which 20 eq. of methylamine (40% in water) are added dropwise and the mixture is stirred at 60-70°C for 6 h. After the reaction has come to an end, part of the ethanol is removed and the product 5 is obtained as a white crystalline solid (yield, 3.45 g as the hydrochloride).

Route 2:

5 g of diketone 6 are initially introduced, as the hydrochloride, in 25 ml of ethanol after which 20 eq. of methylamine (40% in water) are added dropwise and the mixture is stirred at 70-80°C for 6 h. After the reaction has come to an end, part of the ethanol is removed and the product 5 is obtained as a white crystalline solid (yield, 3.87 g as the hydrochloride).

Route 3:

5 g of chloroketone 7 are initially introduced in 25 ml of THF after which 20 eq. of methylamine (40% in water) are added dropwise and the mixture is stirred at 30-40°C for 6 h. After the reaction has come to an end, most of the THF is removed and the product 5 is isolated as a white crystalline solid (yield, 4.10 g as the hydrochloride).

In routes 1-3, aqueous methylamine can also be replaced with gaseous or liquefied methylamine.

Spectroscopic data for the monomethylamino ketone 5 as the hydrochloride:
^{13}C NMR (D_2O, 125 MHz) spin-echo multiplicities in brackets:
δ (ppm)= 188.5 (s), 140.4 (s), 139.2 (d), 137.8 (d), 131.9 (d), 46.9 (t), 37.3 (t), 36.0 (q)
^{1}H NMR (D_2O, 500 MHz):
δ (ppm) = 8.00 (m, 1H), 7.95 (m, 1H), 7.25 (m, 1H), 3.40 (m,2H), 2.75 (m, 2H), 2.62 (s, 3H)

Reduction of compound 5 to give compound 1 (Fig. 1)

NaBH4 (racemic):
5 g of methylamino ketone 5 were initially introduced in 20 ml of ethanol after which 0.8 eq. of NaBH4 was added in portions at 20°C. After the mixture had been stirred for 6 h, it was subjected to aqueous workup. The racemic monomethylaminoalcohol 1 was obtained as a pale yellow solid (yield: 3.9 g)
1H NMR (500 MHz, CDCl3)
δ (ppm)= 2.1 (m, 2H), 2.5 (s, 3H), 2.9 (m, 2H), 4.5 (br s, 2H), 5.25 (m, 1H), 6.94 (m, 1H), 7.00 (m, 1H), 7.22 (m,1H)
13C NMR (125 MHz, CDCl3)
δ (ppm) = 35.4, 36.3, 49.7, 71.4, 122.5, 123.8, 126.6, 149.3

LiAlH4 (chirally modified) carried out as in EP 0457559 A2, example 1B (enantioselectively).

The yield of 1 was 74%, with an enantiomeric purity of 72% ee.